Beef Session

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Does modified-live viral vaccine administration to heifers or cows lack substantial risk?

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Abstract

Modified-live viral (MLV) vaccines are an important tool to limit reproductive loss subsequent to infection from bovine viral diarrhea virus and bovine herpesvirus-1, but are not without risk. Therefore, their utilization must be undertaken with an understanding of the inherent risks of the vaccines and their administration. These risks include the potential causation of undue harm and lack of effective immunization. Consequently, vaccine programs should be designed to minimize the risks while maintaining or maximizing potential benefits of vaccination. The risk of viral transmission from vaccinated calves to naïve cows is low but not absent. Therefore, cows and heifers should be effectively immunized prior to gestation, ideally at least 30 days before breeding. Additionally, revaccination of pregnant cows previously vaccinated with the same MLV vaccine carries a low but detectable risk of adverse reproductive consequences. Understanding the level of risk associated with the vaccination of cattle against bovine viral diarrhea virus and bovine herpesvirus-1 will aid in the optimization of vaccination protocols. Proper timing of MLV vaccine administration can maximize protection against reproductive viral pathogens while minimizing the potential for the development of adverse consequences subsequent to vaccination.

Key words: bovine, cows, vaccine, risks

Résumé

Les vaccins à virus vivants modifiés sont des outils importants pour limiter les pertes en reproduction suite à l'infection des bovins par le virus de la diarrhée virale bovine et l'herpès-virus bovin 1 mais ils ne sont pas sans risque. Par conséquent, leur utilisation doit tenir compte des risques inhérents aux vaccins et à leur administration. Parmi ces risques, les vaccins peuvent causer des dommages indus et immuniser inadéquatement. Les programmes de vaccination devraient donc minimiser ces risques tout en maintenant ou en maximisant les bénéfices potentiels de la vaccination. Le risque de transmission virale d'un veau vacciné à la mère non exposée est faible mais pas absent. Il faudrait donc immuniser adéquatement les vaches et les génisses avant la gestation idéalement au moins 30 jours avant la reproduction. De plus, la revaccination de vaches gestantes vaccinées auparavant avec le même vaccin à virus vivants modifiés comporte un risque faible mais détectable de conséquences néfastes pour la reproduction. Une compréhension du niveau de risque associé à la vaccination des bovins contre le virus de la diarrhée virale bovine et l'herpès-virus bovin 1 sera utile pour l'optimisation des programmes de vaccination. Vacciner au bon moment avec des vaccins à virus vivants modifiés peut maximiser la protection contre des pathogènes reproducteurs viraux tout en minimisant le potentiel de développement de conséquences néfastes suite à la vaccination.

Introduction

Does modified-live viral (MLV) vaccine administration to heifers or cows lack substantial risk when used in specific management situations in the field? As bovine viral diarrhea virus (BVDV) and bovine herpes virus-1 (BHV-1) cause reproductive loss to the cattle industry in the United States, the specific focus of this review will be subcutaneous or intramuscular administration of multivalent, modified-live viral (MLV) vaccines containing BVDV1, BVDV2 and BHV-1. Currently, MLV vaccines are available against BVDV and BHV-1, often in combination with other viral and bacterial antigens. For BVDV, immunization to prevent viremia and birth of persistently infected (PI) offspring is considered important though more difficult to achieve than prevention of clinical disease. While noncytopathic biotypes of BVDV are more prevalent in cattle populations, only cytopathic biotypes are included in the vast majority of MLV vaccine formulations due to safety considerations, as cytopathic strains of BVDV are not considered to result in BVDV persistent infection.[24] Due to the varied field strains of BVDV that may result in fetal infection,

MLV vaccines containing multiple types and subtypes of this pestivirus are expected to provide superior protection against viral challenge.[24] Commercial MLV vaccines containing both BVDV1a and BVDV2 are numerous and generally preferred over the use of monovalent preparations. A meta-analysis[26] and a thorough review[24] focusing solely on vaccination of cattle against BVDV have been published recently.

Infection with BHV-1 can cause endometritis and oophoritis that leads to transient infertility.[21,22] Field infections of pregnant cattle with BHV-1 can result in abortion rates as high as 60%. Late-term abortions may occur up to 100 days after initial infection.[46] Thus, prevention of infertility and abortions due to BHV-1 is considered important. The RLB 106 strain of BHV-1, a temperature-sensitive virus strain capable of replicating in the nasal mucosa but not systemically, is commercially available for intranasal administration.[35] A meta-analysis[25] and a thorough review[3] focusing solely on vaccination of cattle against BHV-1 have been published recently.

In considering risk associated with the administration of MLV vaccines, risk is defined as the likelihood that the vaccine will cause undue harm or lack of effective immunization. When focusing on the potential of vaccination to cause undue harm, the benefit of protection must be weighed against the natural costs and consequences of vaccination which may include stress of cattle due to handling and vaccination, a transient loss in production, and possible injuries to cattle during handling. In appropriately considering the balance of this equation, a critical and accurate assessment should be made of the likelihood that cattle on a specific operation will demonstrate reproductive loss caused by field exposure to BVDV or BHV-1. The prevalence of BVDV within the United States cattle population and the potential to cause reproductive loss appears to be relatively stable, with the average prevalence of 4 PI animals per 1000 head.[12,18,27,28,44] The prevalence of BHV-1 within the United States cattle population and the potential to cause abortion is considered significant, although scrutinized in some geographic areas. A tabular summary of published retrospective analyses of the diagnosis of BHV-1 in cases of bovine abortion submitted to veterinary diagnostic laboratories in North America is presented in Table 1. The prevalence of BHV-1 as the diagnosed cause of bovine abortion decreased notably from 1971 to 1992 (24.38% to 5.41%).[13,14] This precipitous decrease in the prevalence of BHV-1 as the diagnosed cause of bovine abortion was attributed to increased vaccination of open brood cows, appropriate use of modified-live vaccines, and the development of safer effective vaccines.[13] A retrospective analysis of case submissions from 2000 to 2011 demonstrated a slight but significant increase over the study period in the percentage of bovine abortions with BHV-1 as the diagnosed cause.[10] However, this study demonstrated a continued decrease in BHV-1 as the diagnosed cause of bovine abortion in comparison with earlier studies.

In situations where risk may be considered substantial, alternative immunization protocols may be recommended. Considerations of specific management situations in the field include: (a) vaccination of calves nursing pregnant cows that have not been previously vaccinated, (b) vaccination of heifers or cows shortly prior to breeding, (c) vaccination of pregnant heifers or cows that have not been previously vaccinated, and (d) vaccination of pregnant heifers or cows that have been previously vaccinated.

Administration to Calves Nursing Pregnant Cows that have not been Previously Vaccinated

Label precautions for MLV vaccines often include a statement such as "Do not use in calves nursing pregnant

Table 1. Published retrospective analyses of the diagnosis of bovine herpesvirus-1 (BHV-1) in cases of bovine abortion submitted to veterinary diagnostic laboratories in North America.

Year of publication	Dates of case submission	Location of veterinary diagnostic laboratory	Number diagnosed with BHV-1	Number of cases submitted	% diagnosed with BHV-1	Comments	Reference
1973	1971	South Dakota, USA	197	808	24.38%	BHV-1 was most common viral cause.	14
1992	1982-1992	South Dakota, USA	485	8,962	5.41%	BHV-1 was most common viral cause.	13
2004	1983-2001	Michigan, USA	52	1,618	3.21%	BHV-1 was most common viral cause.	43
2013	2000-2011	Iowa, California, Washington, Minnesota, and South Dakota, USA	264	19,459	1.36%	Overall, BHV-1 testing was positive in 3.8% of submissions.	10
2016	2013-2014	British Columbia, Canada	8	236	3.39%	BHV-1 was most common viral cause.	40
2016	2007-2013	California, USA	25	709	3.53%	BHV-1 was most common viral cause.	5

cows unless their dams were vaccinated within the past 12 months as described elsewhere on the label." The risk is that MLV vaccine administration will result in transmission of attenuated viruses from calves to pregnant dams, causing reproductive loss. As available MLV vaccines contain cytopathic strains of BVDV that have not been demonstrated to cause abortions, the true focus of this risk is BHV-1. A study involving subcutaneous administration of MLV vaccine[a] to 18 seronegative steers and heifers in contact with 4 seronegative pregnant control cows on 2 acres did not result in transmission (as indicated by absence of seroconversion of the pregnant cows) or reproductive loss.[15] Initial intramuscular vaccination of 10 seronegative Hereford heifers with an MLV vaccine[b] did not result in detected shedding of BHV-1 or transmission to 9 control herdmates.[4] Clearly, an intranasally administered, modified-live BHV-1 vaccine strain is more likely to be transmitted from vaccinates to contacted cattle than when the same strain is administered parenterally.[20] A recent retrospective field investigation indicated an occurrence of viral transmission and reproductive loss from recently vaccinated and weaned calves to poorly vaccinated cows with which some contact was maintained.[3] While the risk of transmission of attenuated viruses from calves to pregnant dams resulting in reproductive loss appears to be relatively low, the risk clearly emphasizes the need to focus effective vaccination protocols on the stimulation of immunity in heifers prior to their first gestation.

Administration to Heifers or Cows Shortly Prior to Breeding

Due to concerns regarding the safety of MLV vaccines, label precautions include statements such as, "Administer at or about 4 weeks prior to breeding," or "Administer to cows 30 days and heifers at least 60 days prior to breeding." From 1 perspective, administration of MLV vaccine very shortly before breeding appears desirable, as protection from viral reproductive pathogens at, and soon after, the time of breeding is imperative. For many operations, the time of breeding is when cattle from previously separate groups or herds are commingled to increase the size of breeding groups and efficiently achieve pregnancies. This operational strategy creates an opportunity for pathogen transmission to stressed cattle and thus a need for prior effective immunization. Notably, partial protection from clinical disease due to virulent BVDV challenge has been demonstrated in as little as 3 days following a single dose of MLV vaccine, while complete protection against clinical disease due to BVDV may be observed by 5 days following vaccine administration.[2,30] Protection against clinical disease due to BHV-1 has been observed within 2 to 5 days following intramuscular vaccination with MLV vaccines.[33,34,41] Though no vaccine provides complete protection in all circumstances, recent studies using multivalent MLV vaccines have demonstrated consistent BVDV fetal protection rates in the range of 85 to 100% in randomized, controlled clinical trials.[7,9,17,32,42] Recent studies using multivalent MLV vaccines have demonstrated consistent BHV-1 fetal protection rates in the range of 84 to 100% in randomized, controlled clinical trials.[8,9]

Infection with BVDV shortly before the breeding period has the potential to cause oophoritis, particularly diffuse necrosis within corpora lutea, altered ovarian function, endometritis, reduced conception rates, and increased rates of early embryonic death.[3,11,19,23,36] Initial vaccination of naïve heifers with an MLV vaccine very shortly before breeding creates notable risk for negatively impacting reproduction. Initial intramuscular vaccination of 10 seronegative Hereford heifers with an MLV vaccine[b] 3 days prior to synchronized estrus did not result in detected shedding of BHV-1 or transmission to 9 control herdmates.[4] However, after a 35-day breeding season, 6/10 (60%) vaccinated heifers calved compared to 9/9 (100%) unvaccinated controls, which was a significant difference (p=0.034).[4]

In a more recent study, 21 seronegative heifers were vaccinated with killed viral vaccine[c] at 36 and 8 days before synchronized timed artificial insemination (TAI; group1), 7 seronegative heifers were vaccinated with killed viral vaccine[c] at only 8 days before TAI (group 2), 21 seronegative heifers were vaccinated with MLV vaccine[d] at only 8 days before TAI (group 3), and 10 seronegative heifers were maintained as unvaccinated controls (group 4).[31] After TAI, heifers were maintained with breeding bulls for 2 weeks. At 61 days after TAI, ultrasonography revealed pregnancy in 19/21 (90%) group 1 heifers, 6/7 (86%) group 2 heifers, 10/21 (48%) group 3 heifers, and 9/10 (90%) group 4 control heifers. The pregnancy rate in group 3 heifers, which received an initial dose of MLV vaccine only 8 days before TAI, was significantly lower than that of groups 1 and 4. Thus, initial vaccination of naïve (seronegative) heifers with MLV vaccine at 8 days prior to breeding is not recommended due to clear demonstration of reproductive risk.

Notably, the question is often asked about the risk of revaccination with an MLV vaccine shortly before breeding. One study evaluated the impact on conception rates of 799 Angus crossbred heifers when revaccination with an MLV vaccine[e] was performed at 40 days (control group) or 3 days (treatment group) prior to breeding.[1] This revaccination occurred after at least 2 prior doses of MLV vaccine. At approximately 90 days after initial breeding in this estrus synchronization program in which heifers were only artificially inseminated after an observed estrus, ultrasonography revealed an 85.1% conception rate for controls and 86.4% for treatment heifers, which was not significantly different. This study has been critiqued because no unvaccinated animals were maintained in the research design to assess if the third dose of MLV vaccine administered at 40 days prior to breeding had a negative effect on conception rate.[3]

Another study evaluated the impact on pregnancy rates of 692 primiparous dairy cows when an MLV vaccine[f]

or a killed viral vaccine[g] were administered 45 days prior to TAI.[39] This revaccination occurred after 4 prior doses of MLV vaccine. At 60 days after TAI in the double-Ovsynch-TAI protocol, ultrasonography revealed a 43% pregnancy rate for cows administered killed viral vaccine and 44% for cows administered MLV vaccine, which was not significantly different. In this study, revaccination with killed viral vaccine produced higher antibody titers than MLV vaccine for BHV-1 in the primiparous dairy cows which were between 21 and 28 days-in-milk at the time of revaccination.[39]

In a third study focused on revaccination with an MLV vaccine[h] shortly before breeding, 2 groups of 20 seronegative Angus crossbred heifers were vaccinated 2 days after estrus and then revaccinated 30 days later.[37] One group of 20 heifers (Group A) was synchronized in estrus at 10 days after revaccination while the other group (Group B) was synchronized in estrus at 31 days after revaccination. A control group of heifers (n=20) did not receive MLV vaccine. Breeding during this synchronized estrus was achieved by natural service. No differences were detected in the characteristics of estrus behavior assessed using radio frequency technology or embryonic loss assessed using ultrasonography. At 40 days after a 45-day breeding season, 14/20 (70%) Group A heifers were pregnant, 17/20 (85%) group B heifers were pregnant, and 19/20 (95%) control heifers were pregnant. These differences in pregnancy rate were not significant. Thus, while caution is prudent, the likelihood of causing undue harm with revaccination shortly before breeding is notably less than the risk from initial vaccination shortly before breeding. Revaccination with MLV vaccines at no less than 30 days before breeding is recommended by the authors to facilitate optimal reproductive performance.

Administration to Pregnant Heifers or Cows that have not been Previously Vaccinated

Several MLV vaccines now have label approval for the vaccination of pregnant cattle if and only if certain conditions are met (e.g., vaccination of cattle with the same vaccine during the previous 12 months).[24] The fulfillment of these conditions prior to administration of MLV vaccines during pregnancy is critical unless the safety of the vaccination protocol is to depend on the serendipitous field exposure of cattle to BHV-1 prior to pregnancy and vaccination. Vaccination of naïve (seronegative) heifers or cows with MLV vaccine will commonly cause abortion in the following weeks to months.[45] Notably, intranasal administration of an MLV vaccine containing a temperature-sensitive mutant, RLB 106, to pregnant cows has been demonstrated not to cause abortion.[16] Thus, while initial vaccination of pregnant heifers or cows may not cause undue harm in some previously exposed populations, the risk of abortion due to intramuscular or subcutaneous vaccination of naïve cattle during pregnancy with MLV vaccines is high.

Administration to Pregnant Heifers or Cows that have been Previously Vaccinated

Some available MLV vaccines are labeled for administration to pregnant cattle "provided they were vaccinated, according to label directions, with this same product within the past 12 months." To achieve this label claim, which was first approved in 2003, the USDA-APHIS Center for Veterinary Biologics (CVB) requires demonstrated safety studies, including large field trials of approximately 1,200 vaccinates, with some pregnancies at each of the 3 stages of gestation. A publication resulting from 1 set of these safety studies demonstrated that adverse events are rare when label directions are followed.[6] Yet, some risk of abortion when following label directions has been demonstrated in these large field trials. One abortion attributed to BHV-1 occurred in 235 heifers (0.4%) vaccinated with an MLV vaccine according to label directions during the second trimester of gestation.[6] A field investigation indicated an association between vaccination of pregnant cows with an MLV vaccine following label directions and reproductive losses, including BHV-1 abortions.[29] A recent review details multiple published manuscripts that infer a notable impact of this demonstrated, though limited, risk.[3]

As an alternative, a recent study compared the efficacy of annual revaccination of pregnant cows with a multivalent viral vaccine containing temperature-sensitive, modified-live BHV-1 and killed BVDV (combination viral [CV] vaccine[i]) rather than an MLV vaccine[j] after 2 pre-breeding doses of MLV vaccine[j] were initially administered to developing heifers.[38] In this research, cows were challenged during their second gestation through both exposure to PI cattle and subsequent intravenous injection with BHV-1. In unvaccinated control cows, 15/15 fetuses were infected with BVDV and/or BHV-1 while 11/15 (73%) aborted. Pregnant cows revaccinated annually with MLV vaccine[j] demonstrated 2/23 (9%) offspring infected with BVDV and another 2/23 (9%) infected with BHV-1, while 3/23 (13%) were aborted. In comparison, pregnant cows revaccinated annually with CV vaccine[i] demonstrated 0/22 offspring infected with BVDV and 0/22 infected with BHV-1 while 1/22 (5%) were aborted. These differences were significant when comparing the vaccinated groups to the control group. Thus, annual revaccination of previously vaccinated pregnant cows with either an MLV vaccine[j] or a CV vaccine[i] facilitated protection against a rigorous viral challenge.[38]

Conclusions

After careful review of research available from the last 50 years, MLV vaccines containing BVDV and BHV-1 exhibit substantial and commonly unacceptable risk of causing undue harm if administered to previously unvaccinated pregnant heifers or cows, or if administered as the initial dose of MLV vaccine to heifers or cows within 30 days prior to

breeding. Additionally, MLV vaccines exhibit a low risk when administered to calves nursing unvaccinated pregnant cows. When administered to pregnant cows previously vaccinated with the same MLV vaccine, these vaccines exhibit a low but detectable risk of undue harm. Notably, currently available MLV vaccines provide safe and critically effective protection when administered to developing heifers with the last dose administered at least 30 days prior to breeding. In summary, proper timing of MLV vaccine administration can minimize the risk of undesirable side effects while maximizing vaccine efficacy to facilitate the control of disease due to BVDV and BHV-1.

Endnotes

[a]Express 5, Boehringer Ingelheim Vetmedica, Inc., St Joseph, MO
[b]Resbo IBR, Norden/Smithkline Company, Lincoln, NE
[c]ViraShield 6 VL 5 HB, Novartis Animal Health US, Inc., Larchwood, IA
[d]BoviShield Gold FP 5 VL 5, Pfizer Animal Health, Exton, PA
[e]Vista 5 L5 SQ, Intervet, Inc., Millsboro, DE
[f]Express FP 10, Boehringer Ingelheim Vetmedica, Inc., St. Joseph, MO
[g]Triangle 10, Boehringer Ingelheim Vetmedica, Inc., St. Joseph, MO
[h]Express FP 5 VL 5, Boehringer Ingelheim Vetmedica, Inc., St. Joseph, MO
[i]CattleMaster Gold FP5, Zoetis, Florham Park, NJ
[j]Bovishield Gold FP5, Zoetis, Florham Park, NJ

Acknowledgements

Dr. Givens reports grants and personal fees from Boehringer Ingelheim Vetmedica, Inc., grants from Zoetis, Inc., personal fees from Elanco, personal fees from Boehringer Ingelheim Animal Health GmbH, outside the submitted work. In addition, Dr. Givens isolated a novel cytopathic BVDV1b for vaccine production licensed to Pfizer Animal Health, Inc. Dr. Newcomer reports grants from Zoetis, Inc., outside the submitted work.

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